intensity from mild to severe. These GI adverse effects did not occur during placebo administration. In 1 of these 8 patients, the abdominal cramps were accompanied by blurred vision. In 1 patient, headache and drowsiness also occurred. There were no significant changes in vital signs that could be attributed to the mixed micelles. The laboratory safety profile was notable for reductions in hemoglobin and erythrocytes. Furthermore, on the second treatment days of both study periods (days 3 and 16), serum iron was significantly greater ($p < 0.05$) following the mixed micelles infusion than following placebo. Assay of the mixed micelles solution indicated that iron was not a constituent of the infusion mixture. Assay of plasma samples spiked with concentrations of the infusion mixture ranging from ¼-1/1,024, demonstrated no interference with the iron assay. Therefore, the reason for the observed increase in serum iron was unclear.

2. Title: Evaluation of the Safety of Mixed Micelles in Healthy Subjects
Investigator: Drs. Farthing and Ballinger Study site: UK Date of study: 1993
Published in Journal of Parenteral and Enteral Nutrition vol. 20, no. 2, 1996

This was a double-blind randomized, crossover comparison of mixed micelles to placebo. The purpose of this study was to evaluate the safety of mixed micelles at 5 x the daily clinical dose in Cernevit.

2 groups of 6 healthy male subjects, ages 18-50 yrs., mean of 27 yrs., were recruited. Each group of subjects received either placebo (110 ml of isotonic saline) or ~5x the amount of mixed micelles (0.738 g of glycocholic acid dissolved in isotonic saline to a volume of 110 ml) daily for 5 days by IV infusion over 1 hour in a randomized crossover design with a washout period of at least 9 days. Safety was assessed at baseline and during each infusion period by vital signs, routine hematology, biochemistry, UA, serum glycocholic acid, serum haptoglobin and the incidence of adverse events.

Results:

Administration of 5x the clinical dose of mixed micelles was safe and well tolerated. Adverse events were reported in the first treatment period only and occurred in 5 subjects: 3 on placebo and 2 on mixed micelles. On placebo, they were: flatulence, nausea and light-headedness. On mixed micelles, they were heartburn and extravasation at the site of infusion. All of these adverse events resolved spontaneously except heartburn which continued throughout the study and was considered by the investigators to be only remotely related to the administration of the mixed micelles. There was a significant difference between mixed micelles and placebo for glycocholic acid which significantly increased ($p = 0.005$) following mixed micelle administration. This was expected as mixed micelles contain glycocholic acid. Median glycocholic acid levels on placebo were 37.5 ug/dl at baseline and 17 ug/dl post placebo infusion. The corresponding values on mixed micelles were 26.5 ug/dl at baseline and 115 ug/dl post infusion. In 3/12 subjects, the glycocholic acid levels were above the maximum upper limit of 150 ug/dl (170, 410 and 790 ug/dl). The only other statistically significant difference between mixed micelles and placebo was for mean hemoglobin and red blood cell counts which was not clinically relevant.

The investigators state that the liver rapidly clears bile acids from the blood; 10 minutes after injection of labeled glycocholic acid into the superior mesenteric vein, >80% of it is found in the bile. They further state that the detergent properties of bile acids may potentially damage the hepatocyte plasma membrane or even cause cell lysis. Billington and coworkers demonstrated that glycocholic acid causes lysis of isolated hepatocytes at a concentration of 12-16 mmol/l (5.58-7.44 g/l). Lysis of cells, as judged by release of the cytosolic marker enzyme, LDH, was preceeded by release of the plasma membrane enzyme, alkaline phosphatase. In this study, 0.738 g glycocholic acid was infused over 1 hour. Although serum LDH levels were not measured, serum alkaline phosphatase remained within the normal range in all subjects.

3. Title: Comparative Bioavailability Studies with a New Mixed Micelles Solution of Diazepam Utilizing [redacted] Assay, Psychometry and EEG Brain Mapping.
Saletu et al. International Clinical Psychopharmacology 1988, 3, 287-323

15 healthy volunteers (8M and 7F), ages 22-42 yrs. were enrolled in this double-blind, placebo-controlled, cross-over study to compare the PK and PD properties of a standard solution of Valium with those of Valium MM (mixed micelles) solution after IV and IM administration utilizing [redacted] assay, quantitative pharmaco-EEG and brain mapping techniques as well as psychometric and psychophysiological methods. Local tolerance was also evaluated. The subjects received randomized and, at weekly intervals, the following injections: 10 mg Valium IV + placebo IM; 10 mg Valium MM IV + placebo IM; placebo IV + 10 mg Valium IM; placebo IV + 10 mg Valium MM IM and placebo IV +

placebo IM. Blood sampling for PK/PD, EEG, psychometric and psychological tests (Noopsychic tests, Thymopsychic assessments, psychophysiological measures: critical flicker frequency; static and dynamic pupillometry and skin conductance) and tolerance evaluations were carried out at baseline, ½, 1, 2, 4, 6 and 8 hours post drug/placebo administration.

Results:

There were no interformula differences in local tolerances. 6 patients reported pain at the injection site with no significant differences between placebo, Valium or Valium MM. Tiredness was reported in 10, 8, 7, 9 and 6 subjects out of 15 after Valium IV, Valium MM IV, Valium IM, Valium MM IM and placebo. The respective numbers for dizziness were 6, 6, 1, 1 and 1. Other side effects were headache in 1 subject after Valium IV, slurred speech in 1 subject each after Valium IV and Valium MM IM; double vision in 1 subject after Valium MM IV.

The PK/PD results will only be discussed in generalities here as the PK/PD for Valium and Valium MM do not apply to Cernevit. Likewise, effects of Valium on neurophysiological and psychometric/psychological tests, do not apply to Cernevit, a multivitamin preparation.

PK for mixed micelles vs. standard solution:

When administered IM:

Mixed micelles demonstrated a significantly shorter tmax, a higher Cmax and generally higher plasma concentrations in the first and second hour (235 and 220 ng/ml) compared to the standard solution (188 and 167 ng/ml). This suggests better absorption of mixed micelles in the muscle. Peak plasma concentrations were reached at 1.9 hrs. with mixed micelles vs. 3.8 hrs. with the standard solution.

When administered IV:

Mixed micelles demonstrated lower blood levels between 30 min. and 4 hours (289 and 168 ng/ml) than the standard solution (370 and 199 ng/ml).

4. Title: Bioavailability of Three Formulations of Intravenous Diazepam
Fee et al Acta Anaesthesiol Scand 1986: 30: 337-340

The purpose of this randomized, crossover study was to compare the bioavailabilty of 3 formulations of Diazepam (Valium): standard Diazepam (with propylene glycol), Diazemuls (emulsion of Diazepam in soya bean oil and water) and Valium MM (containing lecithin 169.3 mg/ml and glycocholic acid 88.5 mg/ml) administered as a single 10 mg IV injection to 8 healthy volunteers (6M and 2F). Blood samples for PK analysis was obtained up to 24 hrs. post injection.

Results:

Mean plasma levels were significantly higher following Valium injection (2516 ng ml h) than those after Diazemuls (1963 ng ml h) and Valium MM (2152 ng ml h) for all periods analyzed: 0-15 min., 15-60 min. and 1-24 hrs. ($p < 0.05$).

5. Title: A Double-Blind Comparative Study of Three Formulations of Diazepam in Volunteers
Forrest et al Anaesth Intens Care 1988, 16, 158-163

This was a randomized, double-blind, crossover study in 12 male volunteers to compare 3 formulations of diazepam (propylene glycol, mixed micelle and lipid emulsion) for sedation and subsequent recovery. Following IV injection of 10 mg of each formulation, sedation was assessed for 10 min. using a 6 point ordinal sedation score. Subsequent recovery was assessed using a psychomotor/ sedation battery which included a linear analogue sedation scale, letter deletion test, simple reflex time, a simple arithmetic exercise and digital recall.

Results:

Diazepam in propylene glycol was more sedating than the other two formulations and reached peak effect faster than the lipid formulation. These differences between the formulations occurred between 2-7 min. of administration. The authors postulate that Diazepam may be more readily freed from propylene glycol than from the lipid emulsion or mixed micelles vehicles. Subsequent recovery did not differ between the 3 groups. A significant increase in the level of sedation achieved by the preparations was found with each study day indicating that subject or testing factors were also important in determining the sedative response.

The authors conclude that new solvent vehicles, especially the lipid emulsions, primarily affect initial drug efficacy.

6. Title: Increase of Plasma Nonesterified Fatty Acid Concentration and Decrease of Albumin Binding Affinity After Intravenous Injection of Glycocholate-Lecithin Mixed Micelles

Author: Guentert et al J Lab Clin Med 116 (1) 66-75, 1990

The purpose of these studies was two-fold:

1. To determine the effect of mixed micelles (MM) on the bilirubin binding of albumin. This is particularly relevant to the use of MM preparations in newborns because MM contain glycocholic acid which binds to albumin and, therefore, may displace bilirubin from albumin binding sites. This effect was determined using monoacetyldiaminodiphenylsulfone (MADDS), a deputy ligand for bilirubin (i.e. MADDS competes with bilirubin for albumin binding)..
2. To determine the effect of mixed micelles on concentration-time profiles on esterified and nonesterified fatty acids (EFAs and NEFAs), bile acid and palmitate.

6 healthy subjects (3 M and 3 F), ages 26-30 yrs., each received 6 ml (530 mg glycocholic acid) in the form of 2 different MM preparations, MM type I (Vitamin K MM), and MM type II (Valium MM), by IV injection over 2 minutes. The 2 injections were separated by a washout period of 7 days. Blood was drawn at 3, 6, 10, 20 and 60 minutes and 24 hours.

In addition, cord blood was obtained from 6 neonates within 2 minutes of birth.

To determine reserve albumin for binding of MADDS in serum, serum from neonatal cord blood and adult blood was combined with various amounts of MM or glycocholate (maximum amount: 164 ug which yielded a concentration of 351 umol/L glycocholate). Serum collected over the 24 hr. period following IV injection of the 2 MM types was analyzed for bile acid (glycocholic acid), reserve albumin for binding of MADDS, reserve albumin for binding of palmitate, NEFAs and EFAs.

Results:

In vitro results demonstrated that glycocholate alone or as MM, equally displaced MADDS from binding to albumin. The degree of MADDS displacement depended on the amount of glycocholate added. The addition of the maximal dose of glycocholate, 351 umol/L, to neonatal serum resulted in a mean % decrease of 31-35% (mixed micelles and free glycocholate, respectively) in reserve albumin for binding MADDS. The corresponding mean decrease in adult serum was 32% and 31%. However, when 1/3 of this amount of glycocholate or mixed micelles solution was added (117 umol/L which corresponds to a dose of 100 ul Komakion MM to neonates), the reduction in reserve albumin for binding MADDS in serum from neonatal cord blood was relatively modest, ranging from 8%-15% in 5/6 neonates and 23% in the sixth. The reduction in adult serum was also modest.

In vivo results:

These indicated that peak concentrations of bile acids were observed 3 min. after administration of IV MM in all cases. The values declined rapidly thereafter and were near pretreatment levels 20 minutes after injection. Despite higher bile acid content in type II MM, statistically lower bile acid concentrations were observed 3 minutes after administration of this preparation. This effect was more pronounced in males than females.

After MM injection, there was a decrease in reserve albumin for binding of MADDS with a minimum at 3-10 minutes. This effect was more pronounced in males than females with maximum decreases averaging 68% $\pm$ 14% in males and 45% $\pm$ 8.5% in females. Low reserve albumin levels were maintained for 20 minutes.

After MM injection, the concentration of albumin available for binding of palmitate decreased, reaching a minimum in 3-10 minutes. The average maximum decrease was larger for males (60% $\pm$ 23% with range of 26-85%) than females (34% $\pm$ 11% with range of 22-47%). Thereafter, reserve albumin levels increased and were actually higher at 24 hrs. post injection than pretreatment. Binding of FFAs thus appeared to be tighter 24 hours post IV injection of MM.

Following MM injection, serum NEFAs rose markedly, to a greater extent in males (mean $\pm$ SD: 473% $\pm$ 93% with range of 360-593%) than females (mean $\pm$ SD: 148% $\pm$ 91% with range of 26-263%).

On the other hand, a decrease in EFA occurred after MM injection. The maximum decrease was similar for males (mean $\pm$ SD: 21% $\pm$ 4%) and females (mean $\pm$ SD: 18% $\pm$ 12%).

The authors conclude that before drug preparations containing MM are administered to neonates who are at risk of kernicterus, such as premature or SGA infants, the impact of IV MM on bilirubin binding and NEFAs must be investigated.

7. Title: Disposition of Vitamin K After Intravenous and Oral Administration to Subjects on Phenprocoumon Therapy

Author: Oie et al International Journal of Pharmaceutics 43: 223-230, 1988

The objective of this study was to determine the disposition of a new mixed micelle IV vitamin K solution in subjects on anticoagulant therapy and to compare the pharmacokinetics of IV vs. oral dosing of vitamin K.

9 healthy male subjects, between 22-36 yrs. of age, were enrolled in this study. They received phenprocoumon daily in doses titrated to reach a prothrombin complex activity of 15-20% of normal values. This generally took about 10 days. The dose required to do this was then maintained for the remainder of the study. On study days 15 and 29, the subjects received single oral or IV doses of vitamin K MM in a crossover design. The vitamin K MM doses administered were 10, 20, 40 and 60 mg, with 2 subjects receiving one of these four dose levels. (Note: The IV vitamin K dose was diluted to 55 ml with sterile 5% glucose solution. 50 ml of the solution was then infused over 30 minutes. The oral vitamin K MM solution was diluted to 105 ml with water to yield concentrations of 10, 20, 40 and 60 mg/dl vitamin K. 100 ml of the oral solution was ingested with the subjects fasting). PK/PD parameters were assessed up to 36 hr. after IV administration and up to 33 hrs. post oral dosing.

Results:

8 subjects completed the study. Due to personal reasons, 1 subject discontinued the study after completing only the IV part of the study. The IV doses were well tolerated with no observed side effects.

PK of vitamin K after IV and oral dosing:

After IV dosing:

The mean steady-state apparent volume of distribution was 20 $\pm$ 6 L. The mean clearance was 70 $\pm$ 19 ml/min. The mean terminal half-life was 14 $\pm$ 6 hrs. The AUC ranged from 2,970-17,730 mg h/ml. No dose-dependency was detected in any of the PK parameters.

After oral dosing:

No plasma concentration was detected for the first 1-3 hours after oral dosing with the mean lag time being 2.1 $\pm$ 0.8 hours. The plasma concentrations peaked 3-4 hours after oral administration and peak levels ranged from 95- ~1700 ng/ml. The mean terminal half-life was 10 $\pm$ 6 hours. The AUC ranged from 446-10,640 ng. h/ml.

The bioavailability (determined as the ratio AUC oral/AUC IV, adjusted for the difference in dose for each subject) ranged from 3.5% to 60% with mean 33% $\pm$ 20%.

The maximum prothrombin complex activity prior to vitamin K ranged from 15-20% of normal values. After both IV and oral vitamin K administration, the maximum prothrombin complex activity varied substantially in the individual subjects but it correlated statistically significantly with the logarithm of the systemically available dose. The correlation suggests that an amount between 10 and 20 mg must be systemically available to reach a minimum return to 70% of normal anticoagulation.

8. Pharmacokinetics and Tolerance of Intravenous and Intramuscular Phylloquinone (Vitamin K) Mixed Micelles Formulation

Author: Soedirman et al Br J Clin Pharmacol 1996; 41: 517-523

PK and tolerance of vitamin K mixed micelles (Konakion MM) were compared after IV and IM administration. A single 10 mg dose was administered IV over 1 minute or given IM to 31 adult volunteers in an open, randomized, crossover design. There were 16 M and 15 F subjects and age ranged from 21-40 yrs. Subjects were fasting when vitamin K was administered. The interval between the 2 routes of administration was 1-4 weeks. Blood was collected for PK parameters up to 12 hrs. post IV injection and up to 72 hrs. post IM administration.

Results:

There were no reports of systemic or local intolerance after IV administration. 2 patients developed systemic complaints after IM administration. One of these had watery stools and fatigue 12-20 hrs. after IM administration and causal relationship to the test drug was assessed as unlikely. The other patient experienced myalgia of both quadriceps muscles 6-72 hrs. after IM injection into the left quadriceps only. The patient had undertaken a strenuous bicycle tour 1 day prior to the IM injection.

PK after IV administration (n= 30 subjects):

Mean AUC was 1950 ± 450 ng/ml hr with range of 1080-2620;
Mean clearance was 91 ± 24 ml/min
Mean half-life was 3 ± 0.8 hrs.

PK after IM administration (n= 29 subjects):
Mean AUC was 1700 ± 500 ng/ml hr. with range of 580-2340
Mean Cmax was 67 ± 30 ng/ml with time to reach Cmax averaging 9.2 ± 6.6 hrs.

Plasma concentration vs. time profiles of vitamin K after IV administration, were rather homogenous with low inter-subject variability. However, after IM administration, there were considerable differences between subjects. The mean systemic availability of IM vitamin K (Konakion MM), taking into account the longer elimination half-life after IM administration, was 81% ± 14%. However, in ~20% of the subjects, systemic availabilty after IM injection was not optimal, being <65%. . The data suggest irregular and unpredictable absorption after IM as compared to IV administration.

9. Tolerability of a New Vitamin K Preparation for Parenteral Administration to Adults: One Case of Anaphylactoid Reaction.

Author: Havel et al Clinical Therapeutics 9(4): 373-379, 1987

The efficacy (coagulation parameters: e.g. PT, PTT, thrombin time, etc.), safety (hematology profile, liver and renal function and lipids) and tolerability (local and systemic) of a conventional vitamin K preparation containing castor oil as a solubilizer was compared to a new vitamin K compound containing mixed micelles as solubilizer (54.6 mg glycocholic acid and 75.6 mg lecithin).

30 subjects were enrolled in this study. 15 subjects (11 M and 4 F with age range of 25-83 yrs.) were randomized to the conventional vitamin K preparation and 15 (12 M and 3F with age range of 24-85 yrs.) to vitamin K with mixed micelles. Each preparation contained 10 mg vitamin K which was administered by IV injection tid for 4 days.

Results:

The 2 preparations were equally effective. There were no hematological or biochemical effects that could be attributed to either preparation. No local reactions were observed. However, 1 patient, a 44 yr. old M, experienced an anaphylactoid reaction on the second study day, 3 minutes after IV injection over 1 minute of the mixed micelle preparation. The patient became flushed and lost consciousness. His diastolic pressure was <40 mm Hg and he experienced perspiration, wheezing and stridor. He received steroids and antihistamines, as well as calcium and fluid resusitation and recovered within 10 minutes. The patient received no other medication. It is also important to note that the patient received a conventional vitamin K preparation (Konakion) IV for 6 days prior to this study. He tolerated it well with no signs of hypersensitivity.

Intradermal testing with the conventional preparation yielded a positive result within 20 minutes. 8 hrs. post injection of the MM preparation, pruritis and erythema occurred at the site of application. There was no positive skin reaction after intradermal application of the individual components of the 2 preparations. Therefore, sensitivity to pure vitamin K was ruled out. The authors postulate that a new antigen may be formed by vitamin K as hapten plus the emulsifying constituents because no reaction could be obtained by dermal provocation test with the individual components. The authors state this reaction could possibly be nonimmunologically mediated.

10. Comparison of Local Tolerance to Two Diazepam Preparations: Diazemuls and Valium Mixed Micelles in Intravenous Administration

Authors: Charkiolaki et al Acta Anaesth. Hell. J Vol 19, part 2, pp 146-149, 1985

This study compared 2 Diazepam preparations: Diazemuls in which Diazepam is dissolved in an isotonic suspension of oil and water and Valium Mixed Micelles in which Valium is dissolved in bile salts and lecithin. The 2 preparations were compared with regard to both efficacy (mean drug dose needed to achieve anesthesia and time to onset of anesthesia) and tolerance (local and systemic).

100 patients receiving general anesthesia induction were enrolled. They were randomized to either Diazemuls (group 1) or Valium MM (group 2). Mean age of patients in group 1 was 53.6 yrs., and, in the second group, it was 57.5 yrs. The preparations were administered by slow IV injection, with administration to stop when eyelid reflex was suppressed.

Results:

Both preparation were equally efficacious, i.e. they were comparable in mean drug dose needed to achieve induction of anesthesia and the time to achieve anesthesia. Their effect on vital signs (BP, P and RR) were comparable as well as local and systemic tolerance. Regarding local tolerance, the incidence of pain during injection was 10% (5/50) in group 1 and 18% (9/50) in group 2. The incidence of phlebitis/thrombophlebitis was 18% (9/50) in group 1 and 10% (5/50) in group 2. Two patients (4%) in group 1 and one patient (2%) in group 2, experienced a mild and transient allergic reaction (a circumscribed rash on the chest) which was considered not to be significant.

11. Intravenous Premedication with Diazepam

Authors: Mattila ad Suistomaa Anesthesia 1984, vol. 39, pp 879-882

Two preparations of diazepam, Valium Roche Mixed Micelles and Diazemuls were compared for sedative effects and local/systemic tolerance. 119 patients undergoing minor gynecological procedures were enrolled. Patients were randomized to receive either Valium Roche MM or Diazemuls as IV premedication. 10 mg of either preparation was administered by IV injection. The sedative effect was evaluated. The anesthesiologist assessed the ease of injection and any pain caused by the injection. When fully recovered from anesthesia, patients were instructed to observe the site of injection for 14 days for local adverse effects (e.g. edema, erythema, tenderness at the injection site; the degree and duration of severity, etc.).

Results:

60 patients, mean age of 28 yrs., received the Valium Roche MM preparation and 59 received the Diazemuls preparation, mean age of 30 yrs. The sedative effects, as well as local and systemic tolerance, was comparable between the two groups.

12. Local Reactions After Intravenous Injection of Valium Mixed Micelles and Diazemuls

Clemenson et al Ugeskr Laeger 1989; 151:1983-4

The purpose of this study was to compare local venous reactions of Valium Mixed Micelles and Diazemuls.

224 adults patient undergoing lumbar disc surgery were divided into 2 groups: one to receive Valium MM and, the other, Diazemuls in soya bean oil and water). 10 mg of either preparation was administered IV. Pain on injection and symptoms of erythema, tenderness or induration at the injection site that occurred within 24 hrs., were noted. Patients were to report such symptoms up to 2 weeks post injection.

Results:

Of the 224 patients enrolled, 185 actually received injections. 94 patients (50 F and 44 M with age range of 17-79 yrs.) received Valium MM and 91 patients received Diazemuls (37 F and 44 M with age range of 20-75 yrs.).

A total of 22% of patients receiving Valium MM experienced either pain on injection or localized reactions, while the corresponding incidence was 13% in the Diazemuls group. This difference was not statistically significant.

13. Pharmacokinetics and Safety of a New Solution of Vitamin K in Children With Cholestasis

Authors: Manesme et al Journal of Pediatric Gastroenterology and Nutrition 14 (2)160-5, 1992

In this study, 2 formulations of vitamin K were compared: the conventional preparation, Konakion, which contains propylene glycol and castor oil as solubilizers, and a new preparation of vitamin K in a mixed micelles (MM) solution (containing 54.6 mg glycocholic acid and 75.6 mg lecithin). The following parameters were assessed and compared between the 2 preparations:

1. Short-term Safety:

   Local and systemic tolerance and also safety (hematology, Quick test, liver function) before and 7 days after administration of a single 10 mg IM dose of vitamin K, with or without mixed micelles, to 40 infants (20 infants/group), ages 1-6 months, with chronic cholestasis

2. PK of a Single Dose:

   PK of a single dose: 20 mg Konakion orally vs. 20 mg Vitamin K MM orally vs. 10 mg vitamin K MM IM in 9 infants, ages 1-5 mos., with biliary atresia. Also, blood samples were obtained for vitamin analysis at 3, 6, 12, 24 and 48 hrs. and 3, 4, 7 and 14 days after administration. In the 6 patients

receiving the MM solution orally or IM, bilirubin and biliary salts were also measured.

3. Long-Term Safety and PK:

Long-term safety and PK of 10 mg Konakion IM biweekly for 6 mos. to 22 patients vs. 10 mg vitamin K MM solution biweekly either 3 mos. orally (n= 13 patients) or 3 mos. IM (n= 9 patients). The children were 3 mos. – 6 yrs. of age and had chronic cholestasis. Safety was determined by monitoring blood count, Quick value, coagulation factors, liver function, biliary salts, and vitamin K. Blood sampling was performed 14 days after the last administration of vitamin K (i.e. after 6 mos. of Konakion and after 3 mos. with MM) to determine trough levels.

Results:

1. Short-term safety: No adverse effects were observed after IM administration of the MM formulation. There were no significant differences in any of the safety parameters assessed before and after administration of either Konakion or the MM formulation.
2. PK of a single dose:
   Serum vitamin K levels after Konakion administration were low, with peak levels never exceeding 5 ng/ml, indicating low absorption. On the contrary, serum vitamin K levels after administration of the MM preparation were significantly higher, with the highest values occurring after IM administration of MM. This suggests very adequate absorption of vitamin K from the MM solution. No adverse effects occurred and there were no changes in serum bilirubin.
3. Long-term safety and PK:
   There were no significant changes in liver function tests before and after the long-term oral or IM administration of the MM formulation. 2 weeks after the last IM administration, mean serum vitamin K levels were not significantly different ($p > 0.05$) between the standard formulation (8.15 ± 5.39 ng/ml) and the MM formulation (6.71 ± 3.05 ng/ml). However, mean serum vitamin K levels were significantly lower ($p < 0.0005$) 2 weeks after the last oral MM dose (3.02 ± 1.25 ng/ml) compared to that after IM dosing with the standard formulation. Nevertheless, this level is still far above the reference range for serum vitamin K in children (44-1,272 pg/ml with a logarithmic mean of 236 pg/ml). Therefore, the oral MM preparation of vitamin K, can be used in such clinical situations as prophylaxis for late hemorrhagic disease of the newborn because it appears to be equally effective as Konakion .

14. Vitamin K Concentration in Breast-Fed Neonates After Oral or Intramuscular Administration of a Single Dose of a New Mixed-Micellar Preparation of Phylloquinone
Schubiger et al J of Pediatric Gastroenterology and Nutrition 16:435-39, 1993

Plasma vitamin K levels of Konakion MM, Roche, were measured in 25 healthy, breast-fed newborn babies, randomized to receive a single dose of either 1.5 mg IM (11 babies) or 3 mg po (14 babies). Vitamin K levels were measured at 24 hrs, 4 days and 24 days after the single dose administration.

Results:

At 24 hrs., the median plasma vitamin K concentrations were not statistically significantly different between oral and IM dosing. However, at 4 days, the median levels after oral dosing (51 ng/ml) was significantly higher ($p < 0.01$) than after IM dosing (34 ng/ml). After 24 days, the median plasma vitamin K levels had decreased to 0.44 ng/ml (range: 0.19-1.44 ng/ml) in the po group and 1.05 ng/ml (range: 0.37-1.87 ng/ml) in the IM group. These ranges at 24 days in both groups are higher than the reference population of fasting adults (0.17-0.68 ng/ml).

The authors conclude that further studies with oral Konakion MM are needed to determine the dose required to avoid excessive plasma levels and to determine if repeat doses are necessary to prevent hemorrhagic disease of the newborn.

15. Efficacy of Oral Administration of a Micellar Vitamin K Solution in the Neonatal Period
Maurage et al Arch Pediatr 1995, 2:328-332

The aim of this study was to determine if oral administration of a micellar solution of vitamin K at birth would prevent hemorrhagic disease of the newborn.

30 full-term breast-fed infants were enrolled in this study. The control group consisted of 7 infants given, at birth, oral supplementation with a standard vitamin K preparation, Cremophor, 5 mg. 15 other infants received at birth, 3 mg of a micellar solution of vitamin K orally and 8 were given 1.5 mg micellar solution of vitamin K IM. PT activity and plasma vitamin K levels were measured at birth (using cord blood), at 24 hrs. and 1 month after supplementation. CBC with differential and platelet count, SGOT, SGPT and alkaline phosphatase were measured at 24 hrs. of life and at 1 month.

Results:

No hemorrhage occurred and tolerance to vitamin K was good in all groups.

Although an elevated SGOT (> 40 IU/L) was noted in 25/30 infants at 24 hrs., the treatment group these patients were in, was not mentioned. At 1 month, there was no evidence of hepatocellular lysis. 2 infants (one in the control group and one in the oral MM group) had isolated elevations in alkaline phosphatase. There were 5 cases of polycythemia "distributed among the three groups" and 2 cases of anemia at 1 month. In 1 of these infants with anemia (who received oral MM), a transfusion was necessary.

There was no difference among the groups in PT time activity at 24 hrs. or 1 month of life. Only 1 infant had a low PT time activity by 1 month. This infant had received vitamin K MM IM and vitamin K levels were normal. Follow-up PT time activity at 2 mos. was normal with no treatment and an uncomplicated clinical course.

Mean plasma vitamin K levels were higher in the 2 MM groups than in the Cremophor group (1.01 and 1.18 ng/ml after oral and IM MM administration, respectively and 0.86 ng/ml after Cremophor). Only 2 infants had low plasma vitamin K concentrations (this occurred despite normal PT time activity). One of these infants received Cremophor and the low vitamin K level was noted at 1 month (note: this infant had an increase in SGOT at 24 hrs.- 76 IU/L- but a normal PT time activity). The other infant received MM orally. The PT time activity was also low at 24 hrs. in this infant and was associated with an elevated SGOT: 69 IU/L.

In conclusion, the 3 mg oral dose of the micellar solution provided serum vitamin K levels comparable to the other groups.

16. Comparison of Local Tolerance to Valium Mixed Micelles and Diazemuls in Intravenous Administration to Children
Vikas et al Acta Anaesth. Hell. J Vol. 22, Part 1, pp 40-43, 1988

100 children, of both genders, ages 3-13 yrs., who fell within categories I and II according to the ASA classification, were randomized to either Valium MM or to Diazemuls to compare time to onset of anesthesia, mean dose required and tolerance (local and systemic tolerance assessed up to 72 hrs. after the end of anesthesia). A single dose of 0.2 mg/kg was administered IV.

Results:

The mean dose of drug required to induce anesthesia and the mean time to anesthesia induction, were comparable between the 2 formulations. The incidence of pain during the IV administration of the drugs was comparable between the 2 preparations (12% in the Valium MM group and 14% in the Diazemuls group). There was no evidence of phlebitis or thrombosis with either preparation. The 2 formulations were also comparable with regard to vital signs. There were 4 adverse events- 2 with MM and 2 with Diazemuls. In the MM group, the adverse events were nausea in 1 patient and vomiting in another upon awakening from anesthesia. In the Diazemuls group, one patient experienced erythema during anesthesia induction and one had laryngospasm during recovery from anesthesia. These were not associated with special complications.

Clinical Studies to Support the Pediatric Use Subsection of the Product Labeling: